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Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis

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ABSTRACT

Background: Despite growing awareness of the contribution of central pain mechanisms to knee osteoarthritis pain in a subgroup of patients, routine evaluation of central sensitization is yet to be incorporated into clinical practice. The objective of this perspective is to design a set of clinical descriptors for the recognition of central sensitization in patients with knee osteoarthritis that can be implemented in clinical practice.

Methods: A narrative review of original research papers was conducted by 9 clinicians and researchers from seven differente countries to reach agreement on clinically-relevant descriptors.

Results: It is proposed that identification of a dominance of central sensitization pain is based on descriptors derived from the subjective assessment and the physical examination. In the former, clinicians are recommended to inquire about intensity and duration of pain and its association with structural joint changes, pain distribution, behaviour of knee pain, presence of neuropathic-like or centrally-mediated symptoms and responsiveness to previous treatment. The latter includes assessment of response to clinical test, mechanical hyperalgesia and allodynia, thermal hyperalgesia, hypoesthesia and reduced vibration sense.

Conclusion: This article describes a set of clinically-relevant descriptors that might indicate the presence of central sensitization in patients with knee osteoarthritis in clinical practice. Although based on research data, the descriptors proposed in this review require experimental testing in future studies.

Key Words: Knee osteoarthritis, central sensitization syndromes, clinical descriptors, identification

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INTRODUCTION

Knee osteoarthritis is a leading cause of chronic pain, disability and loss of quality of life affecting over 80% of the elderly population.[1,2] While several "pain-generating structures" have been proposed to explain knee osteoarthritis pain,[3] the exact etiology of pain is not well understood.[4] This may be due to the fact that knee osteoarthritis is a whole organ disease with a complex and multifactorial pathophysiology involving structural, psychosocial and neurophysiology factors.[5] Regarding the latter factors, there is strong evidence that central sensitization is a prominent phenomenon in a subgroup of people with knee osteoarthritis,[6,7] especially in women.[8] Central sensitization is a broad concept encompassing numerous and complex pathophysiological mechanisms and is defined as an "*increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input*".[9]

Technically, central sensitization is a neuronal response that can only be measured in animals.[10-12] Currently, a universally accepted term for the phenomenon described as central sensitization in humans is not available and its use in the scientific literature is still under debate.[11-13] In addition, central sensitization is not a yes/no or present/absent single entity or phenomenon but it occurs over a continuum, from a little to a lot. While generally higher in certain chronic pain conditions, pain sensitivity is also along a continuum in these conditions as well.[14,15] In some patient populations, central sensitization may be the characteristic feature of the disorder (e.g. fibromyalgia). In others, such in knee osteoarthritis, not all patients have central sensitization, but only a sub-group.[6] In addition, central sensitization may influence various regions of the body to varying degrees and manifest clinically either in the form of extended

areas of symptoms (i.e. widespread pain in fibromyalgia) or as a more stereotypical region of pain (i.e. referred pain).

Despite growing awareness of the important contribution of central pain mechanisms to knee osteoarthritis pain, routine evaluation of central sensitization is yet to be incorporated into clinical practice. This is likely due in part to the historical laboratory-based focus of central sensitization research, where the equipment and protocols used to identify features of central sensitization (e.g. quantitative sensory testing,[16,17] nociceptive reflex testing,[18] brain neuroimaging techniques[19,20]) are relatively sophisticated, time-consuming, expensive and not well-suited for clinical settings.

The development of patient profiles to subgroup individuals with knee osteoarthritis in terms of pain mechanisms, including those with “dominant” central sensitization pain, is gaining attention in research as reflected by the increasing number of pain phenotyping proposals which have been published in recent years.[21-23] The lack of subgrouping in previous clinical trials has been proposed as an explanation for the modest efficacy of available treatments for knee osteoarthritis.[24] The challenge clinicians face is to determine, in a given individual with knee osteoarthritis , the relative contribution of factors influencing knee osteoarthritis pain,[23,25] including the role of central sensitization .

Currently, there is no widely accepted clinical descriptors to identify “dominant” central sensitization pain in people with musculoskeletal pain including knee osteoarthritis.[10,26] Quantitative sensory testing is a semi-subjective method suggested to be useful in detection of altered pain sensitivity.[27] However, laboratory quantitative sensory testing is not clinically pragmatic and test modalities and protocols are heterogeneous.[27]

The aim of this paper is to provide clinicians with a set of clinical descriptors for the recognition of possible central sensitization in patients with knee osteoarthritis. These descriptors were narratively reviewed by 9 clinicians and researchers from seven different countries by using the current understanding of central sensitization within the context of knee osteoarthritis pain. They are not intended to replace the laboratory-based investigation of central sensitization , but rather to bridge the gap between research findings and clinical practice by translating the clinical and laboratory-based studies of central sensitization in knee osteoarthritis into a broader and more clinically-relevant perspective. This is neither a systematic or exhaustive review of the literature on the role of central sensitization in knee osteoarthritis nor a definitive clinical guidance on what clinicians should do to identify central sensitization, but a summary of possible factors that might indicate the presence of central sensitization in patients with knee osteoarthritis based on supporting evidence.

Clinical descriptors that may aid in identifying a dominance of central sensitization pain in patients with knee osteoarthritis will be structured into two categories for a better overview: descriptors derived from the subjective assessment (subjective descriptors) and descriptors extracted from the physical examination (objective descriptors).

THE SUBJECTIVE ASSESSMENT

Pain intensity and its association with structural joint changes and duration of pain

Individuals with knee osteoarthritis presenting with altered central processing of pain are significantly more likely to report moderate to severe levels of pain.[6,21,28-30] Therefore, a moderate to severe intensity of self-reported knee pain (e.g. pain on a visual analogue scale >5/10[31]) can be a first indicator of central sensitization in knee osteoarthritis. This finding in isolation is however insufficient as moderate to severe intensity of self- reported knee pain defined as >5/10 likely encompasses many cases with and without central sensitization . Additionally, studies reporting an association between higher levels of pain and more pain sensitization[6, 21,28-30] are not clear and consistent regarding whether pain intensity is related to the “worst pain", "usual pain", "current pain" or “pain with movement”.

Unlike severity of pain, the presence of more severe structural changes in the knee joint on imaging is not associated with central sensitization .[2, 21,28] An inconsistent correlation between the degree of structural damage and pain and disability could be an indicator of central sensitization ,[32,33] albeit the discrepancy between structural and clinical findings is well known in osteoarthritisin general.[32] Indeed central sensitization is especially apparent among patients with knee osteoarthritis with high levels of pain but low levels of imaging structural damage.[21,33] The imaging findings most strongly linked to knee pain and disability in people with knee osteoarthritis pain seem to be joint synovitis and bone marrow lesions (identified most readily on MRI imaging).[34-36] Therefore, if clinicians find insufficient evidence of injury or pathology at the

knee that is likely to contribute to the self-reported pain and disability, it may raise suspicion about the presence of central sensitization pain.[37]

Regarding the duration of symptoms, there is controversy in the literature, with some studies reporting an association between a long history of symptoms and central sensitization [21] while others do not.[30] It is assumed that the lack of association between central sensitization and disease duration indicates that some individuals may be predisposed to central sensitization irrespective of the duration of knee osteoarthritis.[30]

Pain distribution

Several methods and instruments have been used to record the patient's pain location and to classify the pattern of knee osteoarthritis pain. The most common method is asking people to draw the area where they feel pain on a body chart.[38-40] Amongst people with knee osteoarthritis, the medial knee region is the most frequently reported pain location,[39,40] though generalized or diffuse knee pain is also commonly reported.[18,40,41]

In relation to knee osteoarthritis, several studies have specifically investigated the association between central pain mechanisms and a widespread distribution of symptom location.[41-46] They concluded that a widespread, non-anatomical distribution of pain seems to be a strong indicator of central sensitization. Accordingly, aggravation and expansion of existing symptoms to sites around and remote to the knee joint may be a clinical sign of central sensitization. Therefore, occurrence of contralateral symptoms, commonly reported by people with knee osteoarthritis, should not be automatically attributed by clinicians to altered weight bearing or biomechanics

due to compensation, as mirror symptoms may also been explained through spinal and supraspinal mechanisms.[47]

To capture and objectify the presence of widespread pain clinicians can calculate the total number of bodily pain sites in a region divided body chart[23,48] or ask the patient to complete a pain drawing (e.g. in a digital tablet) and subsequently compute the total area of pain (e.g. total number of pixels inside the digital chart)[43] (figure 1). Visser et al[45] have recently suggested that calculating percentage pain surface area on a body diagram is an optimal "snapshot" screening tool to identify patients with an increased likelihood of pain sensitization. In particular, subjects with chronic widespread pain defined as a percentage pain surface area ≥ 20% reported high (≥ 19) painDETECT questionnaire scores (suggesting pain "sensitization" or neuropathic pain) compared to control subjects with a lower percentage pain surface area. In additions, significant and independent associations were observed between the presence of chronic widespread pain and Widespread Pain Index score ≥ 7 and painDETECT score ≥ 19.[45]

In summary, clinicians may obtain the area of pain of their patients with knee osteoarthritis using pain drawings and if possible quantify that area, as the presence of extended areas of pain may be an indicator of central sensitization. However, although there have been attempts to define widespread pain which serves as an indicator of central sensitization (e.g. Widespread Pain Index score),[49] there is no validated cutoff score for inferring whether pain is widespread or not.[50]

Behaviour of knee pain

Knee osteoarthritis is commonly associated with pain-at-rest (or stimulus-independent pain) and pain-on-movement (mainly during weight-bearing activities) resulting in difficulties with walking and climbing stairs.[38] In the context of knee osteoarthritis, pain-on-movement is often more severe than pain-at-rest in the early stages of the disease and has an earlier onset in the disease course.[51, 52] There is a growing recognition of the importance of distinguishing between these two types of pain due to different mechanistic pathways and clinical implications.[52, 53]

Pain on-movement has been linked to central sensitization in people with knee osteoarthritis.[54] In particular, increased sensitivity to physical activity (measured by evaluating changes in patient self-reported pain over the course of a 6-minute walk test) is associated with psychophysical indices of central sensitization such as temporal summation of pain.[54] In addition, less exercise induced hypoalgesia/analgesia occurs in different chronic pain populations where central sensitization is a key characteristic as compared to healthy subjects.[55] One could argue therefore that the same would be applicable to the subgroup of patients with knee osteoarthritis where central sensitization is dominant. Previous studies reported normal exercise induced analgesia in patients with knee osteoarthritis following lower[56] and upper body exercises.[57] However, in these studies no attempt was made to classify the patients in terms of pain mechanisms. Rather pressure pain thresholds instead of self-reported pain[54] were used to quantify sensitivity to physical activity. Clinicians may therefore look for a disproportionate self-reported increase in knee pain after

physical activity tests or activity-based interventions to infer the possible presence of central sensitization mechanisms.

Asking about easing and aggravating factors for knee osteoarthritis pain may also be helpful to distinguish between those individuals with either a more dominant nociceptive or central sensitization pain. A clear, proportionate mechanical/anatomical nature to aggravating and easing factors was associated with nociceptive pain in people with low back (± leg) pain.[58] In that same population, a lack of clear proportionate mechanical nature to aggravating and easing factors was considered a predictor sign of central sensitization pain.[59] Therefore a "*disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors*"[59] may indicate the presence of central sensitization pain in people with knee osteoarthritis.

Presence of neuropathic-like or centrally-mediated symptoms

A potential contribution of central sensitization to knee osteoarthritis has been suspected on the basis of patients reporting neuropathic-like[60] or centrally-mediated symptoms (i.e. sleep disturbance, memory changes, general fatigue).[61,62] These symptoms are frequently but not exclusively seen in patients with central sensitization, so they only offer indirect evidence of central sensitization in knee osteoarthritis and need to be integrated into the context of other findings.[63] In particular, two validated questionnaires have shown to be useful for measuring characteristics that indicate altered central nociceptive processing in patients with knee osteoarthritis: the Central Sensitization Inventory[64] and the (modified) painDETECT.[65]

The Central Sensitization Inventoryis a self-reported screening instrument that helps to identify key symptoms associated with central sensitization.[64,66] It is not a direct measure of the actual neuronal phenomenon of central sensitization as its name may infer. The Central Sensitization Inventory evaluates hypersensitivity of senses unrelated to the musculoskeletal system such as noise, heat or cold or bright light and comprises of 25 items each ranged on a 5-point scale with the end points (0) “never” and (4) “always” (range: 0-100). It has high reliability and validity[64] and a cutoff score of 40 out of 100 was able to distinguish between individuals diagnosed with central sensitivity syndromes and a non-patient comparison sample (sensitivity = 81%, specificity = 75%).[67]

Higher scores on the Central Sensitization Inventory are associated with the presence of widespread hyperalgesia in people with knee osteoarthritis.[43] In addition, people with knee osteoarthritis scoring more that 40 (out of 100) before surgery, considered the cuttoff value to affirm that key symptoms associated to central sensitization are present, reported higher pain intensity, lower satisfaction and increased analgesic requirements in the early phase after total knee replacement surgery.[68] This highlights the value of the Central Sensitization Inventory to detect the possible presence of central sensitization and predict poorer outcomes after surgery in people with knee osteoarthritis.

A growing level of evidence suggests that knee osteoarthritis pain has a neuropathic component in some individuals,[69,70] previously approximated to be 30%.[71] Although the painDETECT[19,72] and modified painDETECT[73,74] questionnaires have been used to screen neuropathic-like symptoms in people with knee osteoarthritis, they may also function as measures of characteristics

that indicate augmented central nociceptive processing.[72, 74] Sensitivity, specificity, and positive predictive values of the painDETECT for neuropathic pain symptoms in people with back pain using the cut-off score of 19 were 85%, 80%, and 83%, respectively.[65] Like the original painDETECT, the modified painDETECT is comprised of nine items but with some modifications adapted to people with knee osteoarthritis, such as framing of questions to ask about symptoms 'in or around' the worst knee, over a specific time frame. Therefore, clinicians are encouraged to use this modified version of the painDETECT in patients with knee osteoarthritis.

Details on the features of the Central Sensitization Inventory and (modified) painDETECT questionnaires are presented in table 1.

Psychosocial factors

Psychosocial factors are known to explain some of the variation in pain reporting among individuals with knee osteoarthritis.[75] There is some evidence pointing towards a relationship between maladaptive psychosocial and emotional factors and central sensitization in people with knee osteoarthritis, including pain hypervigilance, pessimism, catastrophism and poor coping strategies.[76-78] However, as data were obtained from cross-sectional studies, firm conclusions regarding causality between cognitive-emotional factors and central sensitization in knee osteoarthritiscannot be drawn. Also maladaptive cognitive-emotional factors may also occur in patients with chronic pain but without central sensitization. At this early stage in this line of research, we feel that maladaptive psychological factors are best regarded as an overlaping but ultimately distinct construct from central sensitization and therefore they have

not been included as clinical indicators of central sensitization among patients with knee osteoarthritis..

Responsiveness to previous treatment

It has been argued that an inconsistent, unpredictable or unsuccessful response to local, nociception-targeted treatments or a strong exacerbation of symptoms severity post-treatment may aid in recognition of central sensitization in patients with chronic musculoskeletal pain.[79] There is evidence that the presence of central sensitization is a prognostic factor for poor outcomes in response to locally-applied physical therapy interventions in some chronic pain conditions such as lateral epicondylalgia[80] or whiplash associated disorders.[81] Although it is conceivable that the presence of central sensitization might also affect physical therapy treatment outcomes negatively in people with knee osteoarthritis, this hypothesis is not yet proven.[82] An inability to endogenously modulate nociception (dysfunctional endogenous analgesia) may explain the disproportionate increase in pain often observed in people with knee osteoarthritis after locally applied interventions (e.g. knee joint mobilization).[83]

Less responsiveness to analgesic and non-steroidal anti-inflamatory pain medications together with better outcomes with administration of some centrally acting drugs (i.e. duloxetine), is another factor that can further consolidate the role of central sensitization in knee osteoarthritis pain.[84] Therefore clinicians are advocated to routinely ask about medications and responsiveness to them.

Persistent post-surgical pain occurs in approximately 20% of patients with knee osteoarthritis after total knee replacement [85] and it has been linked to the presence of central sensitization[86,87] as the purpoted peripheral nociceptive

sources are replaced yet patients still experience persistent pain. An unfavourable symptom outcome after surgery may thus alert clinicians to the potential presence of central sensitization amongst other factors.[86,87] Therefore, assessment of persistent post-surgical pain in a consistent and standardized way by mean for instance of a core outcome set[88] is considered essential for alerting the clinician to the possible presence of central sensitization. Furthermore, the relatively high proportion of patients with persistent pain after total knee replacement highlights the importance of diagnosing central sensitization before patients undergo surgery and revision surgery.[86]

THE PHYSICAL EXAMINATION

Response to clinical tests

Several types of information obtained from the physical examination can be of value in recognizing dominance of central sensitization in individuals with knee osteoarthritispain.[79] In particular, an inconsistent or confusing response to clinical tests applied to the knee joint during the physical examination (i.e. the majority of assessment techniques provoke symptoms), may be suggestive of the presence of central sensitization. This clinical finding has not yet been investigated, but might be plausible based on our current understanding of the mechanism and clinical expression of central sensitization, where nonpainful mechanical stimulus can be interpreted as nociceptive.[16]

Widespread mechanical hyperalgesia and allodynia

Research has shown evidence in support of generalized or widespread hypersensitivity to mechanical stimuli in people with knee osteoarthritis as compared to healthy controls.[6,16,63] Widespread mechanical hyperalgesia is a well-recognized clinical manifestation of central sensitization.[4,16,17] Hyper-responsiveness to mechanical stimuli includes exaggerated responses to pressure and touch. To apply this to clinical practice, lower pressure pain thresholds as assessed by a pressure algometer at sites around (localized pain sensitization) and remote to the knee (widespread pain sensitization) may imply hyperexcitability of central nociceptive pathways. Pressure pain thresholds have demonstrated a good ability to differentiate between people with osteoarthritis and healthy controls at a general population level,[17] but interpretation of pressure pain thresholds within an individual may be challenging due to broad overlap between normal and OA population values. Normative values are available for healthy subjects[89] which could potentially serve as a comparator when assessing patients with knee osteoarthritis. However, normative values are highly variable and depend on the rate of application as well as anatomical location so it may be challenging to determine “non-normal” values.

In the absence of a pressure algometer, the clinician can also use manual palpation (examiner’s thumb) to evaluate widespread mechanical hypersensitivity. A moderate correlation between manual pressure and pressure algometry was found in people with chronic neck pain,[90] albeit the suitability of this to patients with knee osteoarthritis is unknown. Diffuse non-anatomical tenderness on manual palpation is a clinical criterion that was shown to be predictive of central sensitization pain in patients with low back (±leg) pain[59] and chronic neck pain.[90] An expansion of receptive fields, which is characteristic of

central sensitization,[16] may lead to the patient experiencing increased tenderness to palpation well outside of the painful knee joint. A novel alternative to pressure algometry is a spring clamp, as used in a previous study in patients with low-back pain.[91] By placing the spring clamp on the thumbnail for 10 seconds and asking the patients to assess pain intensity, O'Neill et al. were able to assess the pain response of the patients.[91]

The presence of mechanical (tactile) allodynia (pain due to a stimulus that does not normally provoke pain) is associated with knee osteoarthritis[60] and is considered a hallmark sign of central sensitization.[16] Heightened sensitivity to cutaneous light touch can be assessed in the clinical setting using both static or dynamic stimuli by gently touching or brushing/stroking the skin with a cotton wisp, a cotton wool tip or a brush.

Widespread thermal hyperalgesia

Besides widespread mechanical hyperalgesia, greater pain sensititivity to heat [63] and cold stimuli[92] at remote sites from the knee are considered clinical indicators of deficient central processing of nociception in knee osteoarthritis. Hypersensitivity to heat or cold stimuli is normally demonstrated in laboratory conditions by using a computer-controlled thermotester. However, clinical tests for thermal sensitivity have been developed in other chronic pain populations (e.g. chronic neck pain) with good correlations with quantitative measures.[90,93]

When clinically testing thermal sensitivity, the cold or hot item is placed on the skin for some seconds (e.g. 10 seconds[93]) and it should be perceived as cold or hot respectively, but should not elicit pain. If it does trigger pain, then

hypersensitivity to cold or heat is established and the individual can be asked to rate the pain experienced during the test on an numerical rating scale.[90,93] Maxwell and Sterling suggested that pain>5/10 on a numeric rating scale after 10s of ice application may indicate the presence of cold hyperalgesia in whiplash thus aiding in prognosis and treatment decisions.[93]

Hypoesthesia and reduced vibration sense

Hypoesthesia (increased perception threshold) to tactile and vibration stimuli has been found in people with knee osteoarthritis pain, at both local and remote sites from the knee.[60,94] Clinical finding of tactile hypoesthesia adjacent to the injured knee joint has been considered a clinical indicator of central sensitization.[16] When mapping the region of altered sensation, the pattern of sensory deficit in individuals with knee osteoarthritis does not follow a nerve root or peripheral nerve distribution,[16] thus enabling differentiation of sensory changes secondary to nerve injury. For assessing tactile hypoesthesia, the mechanical detection threshold is calculated using calibrated and standardized von Frey utilizing a series of ascending and descending stimulus intensities.[95] As an alternative, the clinician can use a cotton wool or cotton tipped applicator. Typically, assessment is initiated in the area of most pain and the distribution of hypoesthesia is determined by repetitively stimulating the skin, moving outward in a wheel spoke pattern.

Like altered mechanical detection threshold, reduced vibration sense may be indicative of central sensitization in people with knee osteoarthritis.[16] In particular, a reduced vibration detection threshold has been demonstrated in people with knee osteoarthritis at different sites of the lower extremity.[96]

Vibration detection threshold is measured using a biothesiometer or vibrometer, although neither tool is commonly used in a clinical setting. As an alternative, the clinician can use a Rydell Seiffer graded tuning fork placed against different bony sites of the lower extremity[96] (i.e. first metatarsophalangeal joint, medial and lateral malleolus, medial and lateral femoral condyle). The tuning fork can be placed there and record time until the vibration can no longer be perceived by the subject. The presence of any pain with the vibration stimuli can also be recorded. A painful response with testing (vibration allodynia) has been reported as reflecting central nociceptive changes.[16]

Dynamic Measures of Central Sensitization

Temporal summation and conditioned pain modulation are hallmark dynamic measures of central nociceptive hyperexcitability.[4] While these two measures have been routinely used as laboratory measures, their utility as clinical measures may be developed in the future. For instance, temporal summation has been assessed by using von Frey monofilaments.[97] A small spring clamp may be an interesting clinically-applicable measure to assess conditioned pain modulation with a cold pressor test as previously done on patients with back pain.[91]

Table 2 provides a checklist with all the descriptors extracted from the subjective assessment and physical examination that might indicate the presence of central sensitization in patients with knee osteoarthritis.

DISCUSSION

The awareness is growing that central sensitization is of prime importance for the management of patients with knee osteoarthritis, but its classification is challenging since identification of central sensitization is not straightforward and quantitative sensory testing, the most feasible approach for recognizing central sensitization, remains primarily a research tool.[27] Expensive laboratory equipment requiring extensive training make sensory testing methods used to determine the presence of central sensitization impractical for most clinicians. Shorter and less expensive protocols and equipments that permit clinical identification of pain mechanisms including central sensitization in patients with knee osteoarthritis pain are thus needed.[27]

The purpose of this paper was to present a set of less time-consuming and easily applicable clinical descriptors derived from subjective assessment and physical examination that can aid clinicians to recognize dominance of central sensitization in people with knee osteoarthritis pain.. Importantly, these descriptors should not be viewed as unique signs indicating central sensitization, but they can rather be integrated into the clinical reasoning process, since they indicate a possible contribution of central pain mechanisms to knee osteoarthritis, which can affect the appropiate treatment approach for the individual. What is proposed in this paper is at this moment is not a definitive guidance on what clinicians should do to indentify central sensitization but offer interim guidance only. Central sensitization is not a diagnosis nor an illness and therefore it is not suitable for developing diagnostic criteria. The psychometric properties (i.e. inter- and intra-examiner reliability, sensitivity, specificity) of the descriptors proposed in this paper for identifying central sensitization in knee osteoarthritis, either when used alone or in combination,

might be the subject of future research to allow them to be confidently adopted in clinical practice.These descriptors should be viewed as potential candidates that might be tested as future criteria for recognizing central sensitization in people with knee osteoarthritis and their validity as classification tools is still unsubstantiated. Meanwhile, we hope our proposal will facilitate clinicians the acknowledgment and recognition of central sensitization in knee osteoarthritis and eventually adaptation/ improvement of the proposed checklist based on research data.

The presence of central sensitization in knee osteoarthritis has clinical implications for its management. Early identification of dominant central sensitization pain in people with knee osteoarthritis is crucial as the presence of pain sensitization may predict poorer outcomes following physiotherapy treatment[82] or surgery.[86,87] Individuals with knee osteoarthritis pain, where a dominant altered central pain mechanism is demonstrated might benefit from interventions that target central nervous system mechanisms, such as therapeutic pain neuroscience education or cognitive-behavioral therapy (e.g. graded activity and graded exposure),[7] but evidence supporting this notion is lacking. For more indepth guidelines on the treatment of central sensitization in patients with knee osteoarthritis pain, the readers are referred to other sources.[7,98]

CONCLUSIONS

This article presents a set of clinically-relevant descriptors usable during the subjective assessment and physical examination of patients with knee osteoarthritis that might lead the clinician to suspect the presence and severity

of central sensitization. Future studies are needed to empirically test these descriptors and explore their suitability as future criteria for recognizing central sensitization in clinical practice. Clinicians need to be attentive for patients with signs of central sensitization as they might be at risk for unfavourable outcome after locally-applied interventions to the knee. A broader therapeutic approach aiming to desensitize the central nervous system, in contrast to therapeutic modalities that are only directed to structural knee joint pathology, might be more beneficial for these patients.

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Table 1. Questionnaires used for detecting the presence of neuropathic-like or centrally-mediated symptoms in patients with knee osteoarthritis.

Questionnaire	Sub scales	Items	Scoring	Meaninful differences	Remarks
Central Sensitization Inventory	Part A	25 items: (range: 0-100)	≥40/100: useful to identify people with central sensitization syndromes (sensitivity = 81%, specificity = 75%)[67] Severity levels[99]: -subclinical = 0 to 29 -mild = 30 to 39 -moderate = 40 to 49 -severe = 50 to 59 -extreme = 60 to 100	Unknown	Not validated for knee osteoarthritis population: caution when using ≥40/100 to categorically affirm that CS pain is present[68]
	Part B	10 items: yes/no	Not considered for scoring		
painDETECT	None	9 items: (range: -1-38)	Higher scores associated with widespread reductions in pressure pain thresholds[72]	Unknown	
Modified painDETECT	None	9 items: (range: -1-38)	>12/38 associated with signs of CS[73]	Unknown	Includes modifications of the original painDETECT adapted to people with osteoarthritis (e.g. framing of questions)

Abbreviations: CS, Central Sensitization

Table 2. Summary of clinical descriptors extracted form the subjective assessment and physical examination aiding clinicians to recognize central sensitization in patients with knee osteoarthritis.

Descriptors from subjective assessment	Clinical measure	Findings that may indicate CS
Pain intensity Pain intensity *vs* structural damage	VAS/NRS VAS/NRS *vs* imaging techniques	Moderate to severe pain (>5/10) Disproportion between pain intensity and structural damage[32,33]
Pain Distribution	Pain drawings	Enlarged areas of pain outside the knee[43]; mirror symptoms
Behaviour of knee pain	History taking	Disproportionate pain after physical activity[54]/exercise
Neuropathic-like symptoms	painDETECT Modified painDETECT	Higher scores (not specified)[72] >12/38[73]
Centrally-mediated symptoms	Central Sensitization Inventory	>40/100[67]
Responsiveness to previous treatment	History taking	Inconsistent, unpredictable or unsuccessful response to local interventions Poor results with analgesics/AINES; better results with centrally-acting drugs (i.e. duloxetine)[84] Chronic post-surgical pain[86,87]
Descriptors from physical examination	**Clinical measure**	**Findings that may indicate CS**
Response to clinical tests	Clinical orthopedic tests	Inconsistent/confusing response to clinical tests
Mechanical hyperalgesia	Algometer Manual palpation	Widespread, non-anatomical lower pressure pain thresholds[6,16,63] Diffuse non-anatomical tenderness
Allodynia	Cotton wisp/cotton wool tip/brush	Tactile allodynia[16,60]
Thermal hyperalgesia	Ice -10 seconds application[93]	NRS>5/10[93]
Hypoesthesia	Cotton wool/cotton tipped applicator	Local and/or remote tactile hypoesthesia[60,94]
Vibration sense	Rydell Seiffer graduated tuning fork	Reduced vibration detection threshold at different sites of the lower extremity[96] Vibration allodynia[16]

Abbreviations: CS, Central Sensitization; NRS, Numeric Rating Scale; VAS, Visual Analogue Scale.

Figure legends

Figure 1. The area of pain, expressed as the total number of pixels coloured inside a body chart perimeter, presented separately for men and women with knee osteoarthritis pain after superimposing their pain drawings. The colour grid indicates both the number and the percentage of individuals that reported pain in that specific area. Dark red represents the most frequently reported area of pain, while dark blue the least frequently reported area of pain. Reprinted with permission from Lluch Girbés et al.[43]